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Patentanmeldung Nr. Patent application No. Demande de brevet n°

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Method for delivering biologically active substances

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Method for delivering biologically active substances

The present invention relates to a method for releasing a biologically active hydroxyl group containing substance on a substrate and to an aqueous solution containing the reaction product of a biologically active hydroxyl group containing substance, chloroacetyl chloride and a tertiary amine.

U.S. Patent No. 4,083,847 describes transiently water-soluble disperse dyes that contain a group which can be removed under dyeing conditions and which carries at least one water-solubilising group. Addition of large amounts of dispersing agents and stabilizers can thus be avoided.

It has now unexpectedly been found that this principle can be used for the controlled release of biologically active compounds of any kind on various types of substrates by applying a blocked compound in the form of an aqueous solution and later deblocking under hydrolytic conditions.

The present invention relates to a method for the controlled release of a biologically active hydroxyl group containing substance on a substrate, which comprises reacting said hydroxyl group containing substance subsequently with chloroacetyl chloride and a tertiary amine, applying the thus obtained water-soluble aminoacetic acid ester to the substrate and finally hydrolysing the ester on the substrate.

Suitable biologically active hydroxyl group containing substances are any types of drugs, for example pain relief agents like paracetamol and acetylsalicylic acid, vitamins like ascorbic acid, hormones like testosterone and estradiol.

Plant protective agents like herbicides, fungicides, insecticides and bactericides can likewise be used in the method according to the invention.

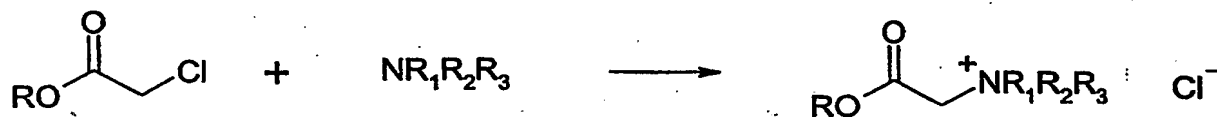
Other suitable biologically active substances are flavouring agents, like menthol and cosmetics.

Other preferred biologically active substances which can be used in the claimed process are insecticides or antimicrobials, like triclosan.

In the first step of the claimed process the hydroxyl group containing substance R-OH is reacted with chloroacetyl chloride thus yielding the corresponding chloroacetic acid ester.



Afterwards a water-soluble ammonium salt is prepared by reaction of the chloroacetic acid ester with a tertiary amine wherein R₁, R₂ and R₃ independently of one another denote organic radicals.



Preferred tertiary amines are the diamines of formula I



wherein R₄, R₅, R₆ and R₇ independently of one another represent C₁-C₁₂alkyl, C₅-C₂₀aryl, C₆-C₂₄aralkyl or C₅-C₂₀cycloalkyl and L is a bivalent aliphatic, cycloaliphatic, aromatic or araliphatic radical.

Examples for suitable diamines of formula I are 1,2-bis(dimethylamino)ethane, 1,3-bis(dimethylamino)propane, 1,2-bis(dimethylamino)propane, 1,4-bis(dimethylamino)butane, 1,3-bis(dimethylamino)butane, 2,3-bis(dimethylamino)butane, 1,5-bis(dimethylamino)-2-pentene, 1,5-bis(dimethylamino)pentane, 1,6-bis(dimethylamino)hexane, 1,7-bis(dimethylamino)heptane, 1,10-bis(dimethylamino)decane, 1,12-bis(dimethylamino)dodecane, 1,2-bis(diethylamino)ethane, 1,3-bis(diethylamino)propane, 1,2-bis(diethylamino)propane, 1,4-bis(diethylamino)butane, 1,3-bis(diethylamino)butane, 2,3-bis(diethylamino)butane, 1,5-bis(diethylamino)-2-pentene, 1,5-bis(diethylamino)pentane, 1,6-bis(diethylamino)hexane, 1,7-bis(diethylamino)heptane, 1,10-bis(diethylamino)decane,

1,12-bis(diethylamino)dodecane, 1,4-bis(dimethylamino)-1,3-butadiene, 1-dimethylamino-2-methyloctylamino-ethane, 1,4-bis(dimethylamino)benzene, 1,4-bis(dimethylamino)naphthalene, 1,6-bis(dimethylamino)naphthalene, 1,8-bis(dimethylamino)naphthalene, 1,4-bis(dimethylaminomethyl)benzene, 1,4-bis(dimethylaminomethyl)naphthalene, 1,6-bis(dimethylaminomethyl)naphthalene, 1,8-bis(dimethylaminomethyl)naphthalene, 1,4-bis(dimethylamino)cyclohexane, 1,2-bis(diphenylamino)ethane, 1,3-bis(diphenylamino)propane, 1,2-bis(diphenylamino)propane, 1,4-bis(diphenylamino)butane, 1,3-bis(diphenylamino)butane, 2,3-bis(diphenylamino)butane, 1,5-bis(diphenylamino)-2-pentene, 1,5-bis(diphenylamino)pentane, 1,6-bis(diphenylamino)hexane, 1,7-bis(diphenylamino)heptane, 1,10-bis(diphenylamino)decane and 1,12-bis(diphenylamino)dodecane.

1,2-bis(dimethylamino)ethane is the preferred diamine of formula I.

The blocked compounds exhibit a high solubility in cold water and accordingly can be applied as aqueous solutions to a variety of substrates like wood, metal, plastics, glass, paper and textile materials.

Preferably, the method according to the invention is used for furnishing textile fabrics.

Suitable substrates are, for example, materials like polyacrylonitril and copolymers of acrylonitrile and other vinyl compounds, e.g. acrylic esters, acrylic amides, vinyl pyridine, vinyl chloride or vinylidene chloride, copolymers of dicyanoethylene and vinyl acetate as well as of acrylonitrile block copolymers, polyurethanes, synthetic polyamides, e.g. poly(hexamethylene adipic acid amide) or polyamide 66, poly(ϵ -caprolactame) or polyamide 6, poly(hexamethylenesebacic amide) or polyamide 610 and poly(11-aminoundecanoic acid) or polyamide 11, cellulose triacetate and cellulose 2½ acetate, polyesters, and in particular all cellulose based substrates like cotton and viscose, and mixed fibers containing cellulose. These materials can be in the most widely differing processed forms, for example spun yarns, knitted fabrics, woven fabrics, yarns or fibres.

The process according to the invention is easy to operate and can be carried out by the conventional methods known in the art of textile dyeing, for example the exhaust process or the padding process.

This application process of the aminoacetic acid ester compound is usually carried out at elevated temperature, for example at 60 °C to 130 °C, if appropriate under pressure, in a slightly acidic, slightly alkaline or neutral bath at a pH of 3 to 8, preferably 4 to 7 and in particular 4.5 to 6. Buffer systems containing, for example, phosphates or carboxylates may be added to the bath.

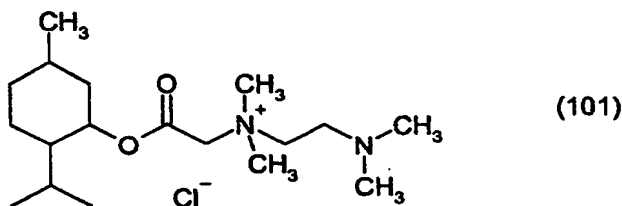
An aqueous solution containing the reaction product of a biologically active hydroxyl group containing substance, chloroacetyl chloride and a tertiary amine is a further object of the invention.

After the treatment with the aqueous solution of the aminoacetic acid ester compound a slow release of the biologically active hydroxyl compound on the substrate starts through hydrolysis. The velocity of this process can easily be controlled through pH and/or temperature variations.

The following examples illustrate the invention.

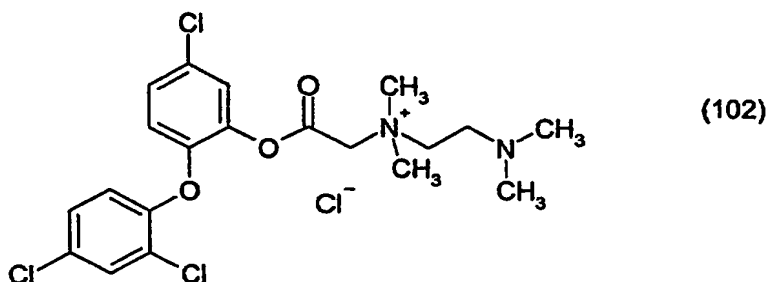
I. Synthesis Examples

I.1. Compound (101)



Menthol is first reacted with chloroacetyl chloride in methyl ethyl ketone/pyridine and subsequently with N,N,N'-tetramethylethylene diamine according to conventional methods to yield the menthol derivative (101).

I.2. Compound (102)



Triclosan is first reacted with chloroacetyl chloride in methyl ethyl ketone/pyridine and subsequently with N,N,N',N' -tetramethylethylenediamine according to conventional methods to yield the triclosan derivative (102).

II. Application Examples

II.1 A sample of 15 g polyacrylonitrile (PAN) fabric (Dralon 5-4301), pretreated with a commercial wetting agent (TINOVETIN[®] JU, supplied by Ciba Specialty Chemicals) at 60 °C during 10 min and rinsed with cold water, is fixed on a support material and in an exhaust dyeing machine of type Ahiba treated with the following composition:

7.5 ml aqueous Na_2SO_4 solution (100 g/l)

2.25 ml aqueous sodium acetate solution (100 g/l)

2.25 ml 80 % acetic acid

233.5 ml water

3.0 ml cationic retarder (TINEGAL[®] MR, Ciba Specialty Chemicals) (100 g/l)

1.5 ml aqueous solution of compound of formula (101) (100 g/l)

The temperature is kept at 98 °C for 20 min; the pH of the bath after cooling to room temperature is 4.7. The sample of PAN fabric is rinsed with cold water and subsequently dried in the air.

Afterwards the PAN sample so obtained is developed in an aqueous 1M- Na_2CO_3 solution. The development can be executed on the entire fabric or merely on parts of the fabric. The odor of menthol is released immediately after the alkaline treatment.

II.2 A PAN fabric (14.9 g) is treated as described in Example II.1 with the following composition:

- 7.5 ml aqueous Na_2SO_4 solution (100 g/l)
- 2.25 ml aqueous sodium acetate solution (100 g/l)
- 2.25 ml 80 % acetic acid
- 232.75 ml water
- 1.5 ml cationic retarder (TINEGAL[®] MR, Ciba Specialty Chemicals) (100 g/l)
- 3.75 ml aqueous solution of compound of formula (101) (100 g/l)

The temperature is kept at 98 °C for 20 min; the pH of the bath after cooling to room temperature is 4.7. The sample of PAN fabric is rinsed with cold water and subsequently dried in the air.

Afterwards the PAN sample so obtained is developed in an aqueous 1M- Na_2CO_3 solution. The development can be executed on the entire fabric or merely on parts of the fabric. The odor of menthol is released immediately after the alkaline treatment.

II.3 A PAN fabric (15 g) is treated as described in Example II.1 with the following composition:

- 7.5 ml aqueous Na_2SO_4 solution (100 g/l)
- 2.25 ml aqueous sodium acetate solution (100 g/l)
- 2.25 ml 80 % acetic acid
- 230.5 ml water
- 7.5 ml aqueous solution of compound of formula (101) (100 g/l)

The temperature is kept at 98 °C for 20 min; the pH of the bath after cooling to room temperature is 5.0. The sample of PAN fabric is rinsed with cold water and subsequently dried in the air.

Afterwards the PAN sample so obtained is developed in an aqueous 1M- Na_2CO_3 solution. The development can be executed on the entire fabric or merely on parts of the fabric. The odor of menthol is released immediately after the alkaline treatment.

II.4 A PAN fabric (14.8 g) is treated as described in Example II.1 with the following composition:

2.25 ml aqueous sodium acetate solution (100 g/l)

2.25 ml 80 % acetic acid

220 ml water

25.5 ml aqueous solution of compound of formula (101) (100 g/l)

The temperature is kept at 98 °C for 20 min; the pH of the bath after cooling to room temperature is 5.2. The sample of PAN fabric is rinsed with cold water and subsequently dried in the air.

Afterwards the PAN sample so obtained is developed in an aqueous 1M- Na_2CO_3 solution. The development can be executed on the entire fabric or merely on parts of the fabric. The odor of menthol is released immediately after the alkaline treatment.

II.5 A cotton fabric is adequately treated with an aqueous solution of compound of formula (102). Subsequent to this treatment, triclosan is slowly released on the fibre, thereby ensuring a good antimicrobial protection over time.

II.6 A cotton fabric is adequately treated with an aqueous formulation of compounds of formula (101) and (102). Subsequent to this treatment, menthol and triclosan are slowly released on the fibre, thereby ensuring both refreshing aromatic fragrance and good antimicrobial protection over time.

Claims

1. A method for the controlled release of a biologically active hydroxyl group containing substance on a substrate, which comprises reacting said hydroxyl group containing substance subsequently with chloroacetyl chloride and a tertiary amine, applying the thus obtained water-soluble aminoacetic acid ester to the substrate and finally hydrolysing the ester on the substrate.
2. A method according to claim 1 wherein the biologically active hydroxyl group containing substance is a drug, plant protective agent, insecticide, antimicrobial, flavouring agent or cosmetics.
3. A method according to claim 2 wherein the biologically active hydroxyl group containing substance is an insecticide or an antimicrobial.
4. A method according to claim 1 wherein the substrate is selected from wood, metal, plastics, glass, paper or textile material.
5. A method according to claim 5 wherein the substrate is a textile fabric.
6. A method according to claim 1 wherein the tertiary amine is 1,2-bis(dimethylamino)ethane.
7. An aqueous solution containing the reaction product of a biologically active hydroxyl group containing substance, chloroacetyl chloride and a tertiary amine.

Abstract

The present application relates to a method for the controlled and/or slow release of a biologically active hydroxyl group containing substance on a substrate which comprises reacting said hydroxyl group containing substance subsequently with chloroacetyl chloride and a tertiary amine, applying the thus obtained aminoacetic acid ester to the substrate and finally hydrolyzing the ester on the substrate.

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